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No. 89-368

IN THE

Supreme Court of the United States

OCTOBER TERM, 1989

MERCK & CO., INC.,

Petitioner,

v.

BIOCRAFT LABORATORIES, INC.,

Respondent.

ON PETITION FOR WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF IN OPPOSITION OF RESPONDENT BIOCRAFT LABORATORIES, INC. TO PETITION FOR WRIT OF CERTIORARI

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STATEMENT PURSUANT TO RULE 28.1

The subsidiaries (except wholly-owned subsidiaries) and affiliates of Respondent Biocraft Laboratories, Inc., are as follows:

None

TABLE OF CONTENTS

	Page
I. INTRODUCTION	1
II. STATEMENT OF THE CASE	2
III. THERE IS NO NEED FOR THIS COURT TO EXERCISE SUPERVISORY AUTHORITY OVER THE FEDERAL CIRCUIT IN THIS CASE	6
A. The Federal Circuit Has Adopted The Correct Analytical Technique In Reviewing District Court Determinations Of The Legal Question Of Obviousness And The Underlying Factual Findings That Must Be Made To Resolve That Question	7
B. The Federal Circuit's Decisions Do Not Conflict With The Patent Laws Nor Undermine Pharmaceutical Research	11
IV. THE FEDERAL CIRCUIT DID NOT VIOLATE RULE 52(a); IT NEITHER IGNORED NOR REWROTE ANY RELEVANT FINDINGS OF FACT	13
A. The Federal Circuit's Opinion Correctly Characterizes The District Court's Findings	14
B. Merck Has Mischaracterized The District Court's Findings Concerning The Properties Achieved By The Claimed Amiloride And Hydrochlorothiazide Combination	16
C. The Federal Circuit Did Not Ignore The District Court's Finding Concerning Merck's Expert Witness	21
D. The District Court Findings Regarding The Methodology Of Pharmaceutical Research And Lack Of Predictability Of Results In The Diuretic Field Are Also Irrelevant	22

E. The Federal Circuit Did Not Ignore The District Court Finding That The Patented Product Was A Commercial Success 23

V. THE FEDERAL CIRCUIT DECISION WILL NOT HAVE AN ADVERSE IMPACT ON PHARMACEUTICAL RESEARCH 24

VI. CONCLUSION 25

TABLE OF AUTHORITIES

CASES	Page
Anderson's-Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57 (1969)	3
Atlantic Richfield Co. v. Interstate Oil Transport Co., 479 U.S. 817 (1986)	7
Bose Corp. v. Consumers Union of United States, Inc., 466 U.S. 485 (1984)	13
Brenda Berkman v. City of New York, ___ U.S. ___, 108 S. Ct. 146 (1987)	7
Carter-Wallace, Inc. v. Otte, 474 F.2d 529 (2d Cir. 1972), *cert. denied*, 412 U.S. 929 (1973)	20
In re Corkill, 771 F.2d 1496 (Fed. Cir. 1985)	13
County of Suffolk v. Arthur V. Graseck, Jr., 480 U.S. 918 (1987)	7
Dennison Mfg. Co. v. Panduit Corp., 475 U.S. 809 (1986)	8,9
Dennison Mfg. Co. v. Panduit Corp., 481 U.S. 1052 (1987)	10
Gerda Dorthea Deweerth v. Edith Marks Baldinger, ___ U.S. ___, 108 S. Ct. 2823 (1988)	7
Graham v. John Deere Co., 383 U.S. 1 (1966)	2,20
Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987)	12
Icicle Seafoods, Inc. v. Worthington, 475 U.S. 709 (1986)	10
Insurance Co. of North America v. Globe Tankers, ___ U.S. ___, 108 S. Ct. 454 (1987)	7
Joseph J. Santacroce, Sheriff of Nassau County v. Herbert Badgley, 479 U.S. 1067 (1987)	7
Kelly v. Southern Pacific Co., 419 U.S. 318 (1984)	16,17

TABLE OF AUTHORITIES-Continued

	Page
Lear Siegler, Inc. v. Aeroquip Corp., 733 F.2d 881 (Fed. Cir. 1984)	11
Leonard M. Freeman v. Heidi Weissman, 58 U.S.L.W. 3219 (U.S. Oct. 2, 1989) (No. 89-114)	7
Newell Cos., Inc. v. Kenney Mfg. Co., 864 F.2d (Fed. Cir. 1988), *cert. denied*, 58 U.S.L.W. 3213 (U.S. Oct. 2, 1989) (No. 88-1936)	8
Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561 (Fed. Cir. 1987)	10,11
Pentec, Inc. v. Graphic Controls Corp., 776 F.2d 309 (Fed. Cir. 1985)	8,11
Ryco, Inc. v. Ag-Bag Corp., 857 F.2d 1418 (Fed. Cir. 1988)	11
Sakraida v. Ag Pro, Inc., 425 U.S. 273 (1976)	3,23
Schutt Mfg. Co. v. Riddell, Inc., 673 F.2d 202 (7th Cir. 1982)	20
Shoe World, Inc. v. El Greco Leather Products Co., ___ U.S. ___, 108 S. Ct. 71 (1987)	8
SmithKline Diagnostics, Inc. v. Helena Laboratories Corp., 859 F.2d 878 (Fed. Cir. 1988)	11,12
Specialty Composites v. Cabot Corp., 845 F.2d 981 (Fed. Cir. 1988)	11
In re Susi, 440 F.2d 442 (C.C.P.A. 1971)	13
Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044 (Fed. Cir.), *cert. denied*, ___ U.S. ___, 109 S. Ct. 75 (1988)	11
In re Vamco Mach. & Tool, Inc., 752 F.2d 1564 (Fed. Cir. 1985)	20
Vladimir Sokolov v. United States, ___ U.S. ___, 108 S. Ct. 1728 (1988)	7
Young Corp. v. Jenkins, 396 F.2d 893 (9th Cir. 1968)	20

TABLE OF AUTHORITIES-Continued

Page

STATUTES

35 U.S.C. § 101 25
35 U.S.C. § 102 25
35 U.S.C. § 103 6,25

RULES

Supreme Court Rule 17.1 6
Fed. R. Civ. P. 52(a) 2,6,7,8,13

OTHER AUTHORITIES

Dwyer, *Legal Affairs*, Bus. Wk., May 22, 1989 12
Gabor, *Breakthroughs May Occur in Labs, but Biotech Money is Made in Court; Fighting Over Splice of Life*, U.S. News & World Report, Nov. 24, 1986 12
Moskowitz, *Technology Owners' Ace in the Hole*, Chem. Wk., Mar. 4, 1987 12
Perry, *The Surprising New Power of Patents*, Fortune, June 23, 1986 12
Sobel, *The Court of Appeals for the Federal Circuit: A Fifth Anniversary Look at its Impact on Patent Law and Litigation*, 37 Am. Univ. L. Rev. 1087 (1988) 12

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I. INTRODUCTION

In its Petition, Merck portrays the Federal Circuit as a runaway court that disregarded the clearly erroneous standard of Fed. R. Civ. P. 52(a) in reversing the district court decision, ignored the findings of the district court, wrote new findings, and deviated from its own precedents as well as those of this Court in reaching the legal conclusion that U.S. Patent No. 3,781,430, Merck's patent in suit (the '430 patent), was invalid. Incredibly, it contends that the Federal

Circuit's actions in this case will adversely impact on future pharmaceutical research. The Federal Circuit, however, was guilty of none of these sins. It accepted the relevant findings of the district court. Thus, the clearly erroneous standard of Rule 52(a) is not an issue. Not a single relevant finding of the district court was ignored and no new findings were written. Moreover, the decision is fully consistent with the decisions of this Court and the Federal Circuit's prior precedents. It will have no discernible impact on pharmaceutical research. In short, the Petition is full of rhetoric but little substance. It should be denied.

II. STATEMENT OF THE CASE

Merck has attempted to portray the development of Moduretic® as long and arduous, and characteristic of pharmaceutical research. (Petition at 8-9.) Merck's history, however, presents a distorted picture. It relies on work performed at Merck during the late 1950's and early 1960's, all of which is irrelevant since the prior art reference upon which the Federal Circuit's invalidity holding is based became available in 1964. *Cf. Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966) (unsuccessful attempts to reach a solution to problem solved by invention occurring before availability of prior art are "wholly irrelevant"). As will be demonstrated below, this single prior art reference taught combining the two compounds found in the composition claimed in the '430 patent for the very same purpose as they are combined in the '430 patent. In fact, the district court found that the composition claimed in the '430 patent achieved precisely the results taught by the prior art reference.

The facts found by the district court in this case thus present a more compelling case of obviousness

then was found in *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 281-82 (1976), and *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57 (1969), wherein this Court held that a combination of old elements is unpatentable if each of the elements performs its known function and the combination does not achieve an unexpected result. Consequently, the Federal Circuit's reversal of the district court's validity determination was legally sound. Those prior precedents are particularly compelling here because the prior art patent was owned by Merck and provided Merck with 17 years of patent protection for the very same subject matter that is covered by the '430 patent. Thus, we are here faced with a situation where Merck is attempting to extend the period of exclusivity by obtaining two patents for one patentable invention.

The genesis of the subject matter of the '430 patent is a discovery by Merck's scientists that a group of pyrazinoylguanidines, one of which was amiloride, had beneficial diuretic properties that caused the urinary excretion of sodium, but not potassium, and when coadministered with certain other diuretics, such as hydrochlorothiazide, prevented the undesirable loss of potassium caused by these other diuretics. These pyrazinoylguanidines, including amiloride, were disclosed and claimed in prior art U.S. Patent No. 3,313,813 (the '813 patent).[1] The disclosure of the prior art '813 patent, which became available in 1964, expressly taught that each of the disclosed pyrazinoylguanidines would cause sodium excretion without also causing potassium excretion and that each pyrazinoylguanidine would prevent the loss of potassium caused by

[1] Merck submitted copies of the '813 patent to the Court at the time it filed its Petition.

a potassium losing diuretic. (Col. 3, ll. 10-22.) The patent expressly identified amiloride as a pyrazinoylguanidine and hydrochlorothiazide as a potassium-losing diuretic. (Col. 49, Examples 207 and 208.)

The '430 patent claims a combination of amiloride and hydrochlorothiazide in specified ratios or amounts. The patent itself alleges that the combination of amiloride and hydrochlorothiazide produced the unexpected result of causing more sodium excretion than would have been expected from the sodium excreting properties of the individual compounds. Indeed, it was this allegation—which the district court found was incorrect with respect to the specific combination patented—that induced the Patent and Trademark Office (PTO) to grant the '430 patent. More specifically, while the applications leading to the '430 patent were before the PTO, they were rejected as obvious over the '813 patent. The '430 patent issued *only* after Merck submitted evidence which allegedly demonstrated that the combination produced an unexpected level of sodium excretion in animal and human studies.

Merck, however, did not disclose to the PTO that its scientists had concluded, after years of testing, that the alleged unexpected increase in sodium excretion was obtained only when the amount of amiloride was so high that it caused the retention of too much potassium and was therefore unsafe. As the testimony of Merck's Medical Director in charge of the clinical testing of the amiloride-hydrochlorothiazide combination established, those scientists had concluded that a meaningful increase in the sodium excretion was not obtained when 5 mg. of amiloride was co-administered with 50 mg. of hydrochlorothia-

zide. (App. E at 6a-14a.) That evidence is significant because that is the composition that both Merck and Biocraft sell and which is covered by every one of the '430 patent claims.

The district court found that the combination of amiloride and hydrochlorothiazide was one of approximately 1,200 combinations of a pyrazinoylguanidine and a potassium-losing diuretic disclosed in the '813 patent, but that neither amiloride nor hydrochlorothiazide was indicated to be preferred. (App. B at 30a.) It further found that the '813 patent did not suggest the properties which the '430 patent *alleged* were obtained by the amiloride-hydrochlorothiazide combination. (App. B at 29a.) It therefore held that the claimed composition was merely obvious to try (App. B at 26a), *even though it also found that the claimed composition of 5 mg. amiloride and 50 mg. of hydrochlorothiazide merely achieved the results described in the prior art '813 patent and not the unexpected property described in the '430 patent*, that is, it merely caused a decrease in potassium excretion, without also causing a decrease in sodium excretion. (App. B at 18a.)

In the decision attacked by Merck, the Federal Circuit found that the district court committed an error of law. It ruled that, when the teachings of the '813 patent, as found by the district court, are considered in conjunction with the properties *actually achieved* by the claimed composition (as opposed to those *alleged* in the '430 patent), the claimed invention would have been obvious to a person of ordinary skill in the art and not, as the district court found, merely obvious to try. That holding was fully consistent with the prior precedents of this Court and was based upon

the factual findings actually made by the district court. As will be demonstrated below, that decision did not violate Rule 52(a). As a result, there is no need for this Court to exercise its supervisory authority and grant certiorari to review this case.

III. THERE IS NO NEED FOR THIS COURT TO EXERCISE SUPERVISORY AUTHORITY OVER THE FEDERAL CIRCUIT IN THIS CASE

The rules of this Court provide that review by way of writ of certiorari "will be granted only when there are special and important reasons therefor." (Rule 17.1.) Merck asserts that this Court should exercise its supervisory authority over the Federal Circuit to ensure (1) compliance with Rule 52(a), Fed. R. Civ. P., in reviewing obviousness determinations made by the district courts, and (2) that 35 U.S.C. § 103 is applied in a manner which does not undermine pharmaceutical research. (Petition at 17-27.) Given the facts of this case, neither reason meets the criteria of Rule 17.1.

As will be demonstrated below, the Federal Circuit has adopted an analytical technique in determining the legal question of obviousness which recognizes that the factual inquiries underlying that legal conclusion must be considered under the clearly erroneous standard of Rule 52(a). Moreover, in this case, Rule 52(a) is not even implicated since the Federal Circuit accepted all the factual findings of the district court and did not, as Merck alleges, engage in a de novo review of those facts. It will also be shown that it is absurd for Merck to assert, as it does in its Petition, that Federal Circuit decisions are somehow undermining research efforts in the pharmaceutical or any other industry.

A. The Federal Circuit Has Adopted The Correct Analytical Technique In Reviewing District Court Determinations Of The Legal Question Of Obviousness And The Underlying Factual Findings That Must Be Made To Resolve That Question

Merck is not the first petitioner to contend that the Federal Circuit has failed to adhere to the clearly erroneous standard of Rule 52(a). Indeed, that is the common complaint of many petitioners who are dissatisfied with the decisions of the Courts of Appeals.[2]

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[2] In an effort to support is assertion that the Federal Circuit disregards the mandate of Rule 52(a), Merck cites fourteen petitions for certiorari, all of which have been denied, in which petitioners alleged that the court had violated Rule 52(a). Those citations merely demonstrate that the losing party will often complain that the appellate court failed to adhere to the clearly erroneous requirement. This is amply demonstrated by the fact that at least nine petitions for certiorari from the Second Circuit were filed during the same period and make similar allegations. *Atlantic Richfield Co. v. Interstate Oil Transport Co.*, 479 U.S. 817 (1986) (*cert. denied*); *Joseph J. Santacroce, Sheriff of Nassau County v. Herbert Badgley*, 479 U.S. 1067 (1987) (*cert. denied*); *County of Suffolk v. Arthur V. Graseck, Jr.*, 480 U.S. 918 (1987) (*cert. denied*); *Brenda Berkman v. City of New York*, ___ U.S. ___, 108 S. Ct. 146 (1987) (*cert. denied*); *Shoe World, Inc. v. El Greco Leather Products Co.*, ___ U.S. ___, 108 S. Ct. 71 (1987) (*cert. denied*); *Insurance Co. of North America v. Globe Tankers*, ___ U.S. ___, 108 S. Ct. 454 (1987) (*cert. denied*); *Vladimir Sokolov v. United States*, ___ U.S. ___, 108 S. Ct. 1728 (1988) (*cert. denied*); *Gerda Dorothea Deweerth v. Edith Marks* Baldinger, ___ U.S. ___, 108 S. Ct. 2823 (1988) (*cert. denied*); *Leonard M. Freeman v. Heidi Weissmann*, 58 U.S.L.W. 3219 (U.S. Oct. 2, 1989) (No. 89-114) (*cert. denied*). Significantly, in *Insurance Co. of North America*, the petitioner urged, in language strikingly similar to Merck's:

> The court of appeals decision in this case is yet another instance of the Second Circuit's practice of

This Court has already granted a petition for certiorari to address a contention that the Federal Circuit ignored Rule 52(a) "in substituting its view of factual issues for that of the District Court." *Dennison Mfg. Co. v. Panduit Corp.*, 475 U.S. 809, 810 (1986). In granting that petition, this Court summarily vacated the Federal Circuit's judgment and remanded the case to that court, stating:

> The Federal Circuit . . . did not mention Rule 52(a), did not explicitly apply the clearly-erroneous standard to any of the District Court's findings on obviousness, and did not explain why, if it was of that view, Rule 52(a) had no applicability to this issue. We therefore lack an adequate explanation of the basis

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exceeding its authority under Rule 52 of the Federal Rules of Civil Procedure by disregarding the trial court's findings of facts. [Petition at 5.]

Similarly, Merck's reliance on four dissenting or concurring opinions and two publications which allegedly complained that the Federal Circuit engaged in fact finding does not justify granting certiorari. Similar dissents and articles can no doubt be found in every circuit. Moreover, two of the four opinions have no bearing on the issue presented by Merck. In *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309 (Fed. Cir. 1985), the concurring opinion did not even suggest that the Federal Circuit had not abided by Rule 52(a). To the contrary, the writer stated: "I agree with the majority that the findings of fact in this case withstand scrutiny under such [clearly erroneous] standard of review." 776 F.2d at 319. In *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757 (Fed. Cir. 1988), *cert. denied*, 58 U.S.L.W. 3213 (U.S. Oct. 2, 1989) (No. 88-1936), the appeal was from a jury verdict and thus Rule 52(a) was not in issue. In fact, Judge Newman, in dissent, expressly stated that the majority's analytic technique would have been appropriate in a bench trial because of the applicability of Rule 52(a). 864 F.2d at 781.

> for the Court of Appeals' judgment: most importantly, we lack the benefit of the Federal Circuit's informed opinion on the complex issue of the degree to which the obviousness determination is one of fact.

475 U.S. at 811.

On remand, the Federal Circuit clearly articulated the interplay of fact and law in the obviousness determination and the applicability of the clearly erroneous standard to that analysis. The court stated:

> On review of a judgment based on a conclusion of obviousness under 35 U.S.C. § 103, this court must consider not only whether there is legal error, but also whether the underlying findings are either nonprobative, or clearly erroneous, or both. If, unlike the present case, a district court had not made findings necessary to resolution of the § 103 question, and legal error were present, an appellate court would vacate in view of that legal error and remand for the district court to make the missing findings. *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 872-75, 228 USPQ 90, 97-99 (Fed. Cir. 1985). If unassailable findings were made but could not support the appealed judgment under a proper application of law, an appellate court may vacate or reverse but not make its own findings. *Icicle Seafoods, Inc. v. Worthington*, U.S. ___, ___, 106 S.Ct. 1527, 1530, 89 L.Ed.2d 739, 743 (1986).
>
> . . . .

> To obtain reversal without remand, an appellant-patentee must convince this court that the patent challenger failed at trial to carry its statutory burden, 35 U.S.C. § 282, of proving by clear and convincing evidence sufficient facts to support the obviousness conclusion. One way to do that is to show that a proper application of the law to unassailable findings compels reversal. Another is to show that the findings on which the obviousness conclusion rested are clearly erroneous and that nothing of record warrants a further exercise of the fact-finding function or indicates any possibility that the appealed judgment might be sustained by such exercise.

Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1565-66 (Fed. Cir. 1987), footnotes omitted.

This Court, apparently satisfied with this analysis, denied certiorari of the Federal Circuit's remand decision. *Dennison Mfg. Co. v. Panduit Corp.*, 481 U.S. 1052 (1987).

Indeed, the analysis is fully consistent with the following guidelines set forth in *Icicle Seafoods, Inc. v. Worthington*, 475 U.S. 709, 714 (1986):

> If the Court of Appeals believed that the District Court had failed to make findings of fact essential to a proper resolution of the legal question, it should have remanded to the District Court to make those findings. If it was of the view that the findings of the District Court were "clearly erroneous" within the meaning of Rule 52(a), it could have set them aside on that basis. If it be-

> lieved that the District Court's factual findings were unassailable, but that the proper rule of law was misapplied to those findings, it could have reversed the District Court's judgment.

The Federal Circuit had recognized, prior to the *Panduit* remand decision, that while the conclusion of obviousness is a matter of law, the correctness of the factual findings upon which that legal conclusion is based must be reviewed under the clearly erroneous standard of Rule 52(a). *See Lear Siegler, Inc. v. Aeroquip Corp.*, 733 F.2d 881, 887 (Fed. Cir. 1984); *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 313 (Fed. Cir. 1985). It has adhered to that standard after the *Panduit* remand. *See Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1050 (Fed. Cir.), *cert. denied*, ___ U.S. ___, 109 S. Ct. 75 (1988); *Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 989 (Fed. Cir. 1988); *Ryco, Inc. v. Ag-Bag Corp.*, 857 F.2d 1418, 1423 (Fed. Cir. 1988); *SmithKline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 886 (Fed. Cir. 1988).

In this case, the Federal Circuit adhered to that analytical technique. It accepted the findings of the district court, but reversed because the proper rule of law was misapplied to those findings.

B. The Federal Circuit's Decisions Do Not Conflict With The Patent Laws Nor Undermine Pharmaceutical Research

It is difficult to believe that Merck can seriously charge that the decisions of the Federal Circuit are somehow inconsistent with the patent laws and may undermine pharmaceutical research. After all, it is well recognized in both the legal and lay communities

that the Federal Circuit has had a positive impact on the value of patents. *See* Sobel, *The Court of Appeals for the Federal Circuit: A Fifth Anniversary Look at its Impact on Patent Law and Litigation*, 37 Am. Univ. L. Rev. 1087, 1089-92 (1988) ("a climate more favorable to upholding the validity and particularly the non-obviousness of patents has emerged"; "the court has brought about a philosophical change which strengthens the patent system."); Dwyer, *Legal Affairs*, Bus. Wk., May 22, 1989, at 78, 79; Moskowitz, *Technology Owners' Ace in the Hole*, Chem. Wk., Mar. 4, 1987, at 22, 23-24; Gabor, *Breakthroughs May Occur in Labs, but Biotech Money is Made in Court; Fighting Over Splice of Life*, U.S. News & World Report, Nov. 24, 1986, at 52; Perry, *The Surprising New Power of Patents*, Fortune, June 23, 1986, at 57, 60.

With specific reference to the pharmaceutical industry, the Federal Circuit has not hesitated to uphold patents in the pharmaceutically related areas. See *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987), *SmithKline Diagnostics, supra.*

Moreover, the decision below provides no disincentive for pharmaceutical research. Merck's research efforts which led to the discovery of amiloride and its use in combination with hydrochlorothiazide were fully rewarded by the grant of the '813 patent. The Federal Circuit ruling in this case is thus quite narrow. It merely holds that, given the teachings of the '813 patent that numerous compositions, including one composed of amiloride and hydrochlorothiazide, have desirable diuretic properties, a second patent covering a composition of amiloride and hydrochlorothiazide

cannot be obtained unless the combination produces unexpected results. That has long been the law.[3] Thus, Merck's suggestion that the Federal Circuit is somehow undermining pharmaceutical research has no basis in fact.

IV. THE FEDERAL CIRCUIT DID NOT VIOLATE RULE 52(a); IT NEITHER IGNORED NOR REWROTE ANY RELEVANT FINDINGS OF FACT

Contrary to Merck's repeated assertions, this is not a case where Rule 52(a) is implicated. Here the Federal Circuit accepted all of the district court findings of fact. The appellate court reversed the district court's decision only because it found that the district court's "conclusion that obviousness had not been proven is incorrect as a matter of law." (App. at 5a.) The Federal Circuit was, therefore, not constrained by the clearly erroneous standard of Rule 52(a). *Bose Corp. v. Consumers Union of United States, Inc.*, 466 U.S. 485, 501 (1984) ("Rule 52(a) does not inhibit an appellate court's power to correct errors of law, including those that may infect a so-called mixed finding of law and fact . . .").

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[3] *See In re Corkill*, 771 F.2d 1496, 1500 (Fed. Cir. 1985) (obviousness rejection of claims affirmed in light of prior art teaching that "hydrated zeolites will work" in detergent formulations, even though "the inventors selected the zeolites of the claims from among 'thousands' of compounds"); *In re Susi*, 440 F.2d 442, 445 (C.C.P.A. 1971) (obviousness rejection affirmed where the disclosure of the prior art was "huge, but it undeniably include[d] at least some of the compounds recited in appellant's generic claims and it is of a class of chemicals to be used for the same purpose as appellant's additives").

A. The Federal Circuit's Opinion Correctly Characterizes The District Court's Findings About The Disclosure Of The '813 Patent

The centerpiece of the Petition is the unfounded allegation that the Federal Circuit rewrote a key finding of the district court concerning the disclosure of the '813 patent. (Petition at 5-6, 11-12, 15-16.) In support of its position, Merck focuses on a single sentence and ignores the remainder of the fourteen page opinion. The limited focus and the resultant removal of the sentence from the context of other relevant portions of the opinion has totally distorted the meaning of the sentence in question.

The Federal Circuit decision states, in pertinent part, that:

> The district court found that the combination of amiloride and hydrochlorothiazide was disclosed in the '813 patent. 690 F. Supp. at 1383. Further finding that more than 1200 combinations are disclosed and that neither amiloride nor hydrochlorothiazide are highlighted as preferred embodiments of the '813 patent, however, the district court concluded that the combinations claimed in the '430 patent would merely be "obvious to try," and therefore not barred by 35 U.S.C. § 103. We do not quarrel with the factual findings of the district court, but we believe its conclusion that obviousness had not been proven is incorrect as a matter of law.
>
> . . . .
>
> That the '813 patent discloses a multitude of effective combinations does not render any

> particular formulation less obvious. [App. A at 5a-6a.]

The Federal Circuit was thus not stating that the district court had found that the combination of amiloride and hydrochlorothiazide was uniquely disclosed. It was instead stating that the district court found that the combination was one of 1,200 possible described combinations.[4] That is precisely what the district court found when it stated:

> Since the '813 patent discloses in excess of 120 pyrazinoylguanidine [sic] and 10 possible potassium losing diuretics, there are more than 1200 possible combinations, of which the combination of Amiloride and Hydrochlorothiazide would be one. [App. B at 30a.]

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[4] Merck erroneously contends that Biocraft had conceded that the district court had not found that the combination of amiloride and hydrochlorothiazide had been disclosed in the '813 patent. (Petition at 6.) That assertion, however, mischaracterizes Biocraft's position. Before the district court and the Federal Circuit, Biocraft was arguing that because the '813 patent *highlighted* three specific pyrazinoylguanidines, one of which was amiloride, and only one potassium-losing compound, hydrochlorothiazide, that patent described *three* combinations of a pyrazinoylguanidine and a potassium-losing compound, one of the three being amiloride and hydrochlorothiazide, in a unique manner. The district court, in holding that the '813 patent did not indicate a *preference* for either amiloride or hydrochlorothiazide, rejected that contention. The Federal Circuit did not reject the district court finding that there was no preference. It merely held that the lack of such a teaching was irrelevant since, for the purpose of the obviousness analysis, it was not necessary that the amiloride-hydrochlorothiazide combination be described as a preferred composition. (App. A at 6a-7a.)

B. Merck Has Mischaracterized The District Court's Findings Concerning The Properties Achieved By The Claimed Amiloride And Hydrochlorothiazide Combination

Merck grossly mischaracterizes the district court's findings when it alleges that the claimed combination produced an unexpected increase in sodium excretion and that, when "fairly read," the district court's opinion demonstrates that it found that such unexpected results were achieved. (Petition at 12 n.5, see also Petition at 7, 9, 19.) The district court specifically rejected Merck's contention that the patented combination produced an unexpected increase in sodium excretion. (App. A at 9a.) It instead found that the claimed combination only "results in a reduction in the amount of potassium ions that are eliminated, *without a reduction in the amount of sodium ions that are eliminated.*"[5] (App. B at 18a.)

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[5] Merck, relying on *Kelly v. Southern Pacific Co.*, 419 U.S. 318 (1984), asserts that it was error for the Federal Circuit to rely upon the district court's failure to adopt a proposed finding in stating that the trial court had found that the amiloride-hydrochlorothiazide combination did not cause a more than additive increase in sodium excretion. (Petition at 19 n.11.) *Kelly* is, however, inapposite. In that case, the court of appeals apparently based its conclusion that there was no employment relationship between the parties solely on the district court's failure to adopt proposed findings of the petitioner. 419 U.S. at 325, 331-32. In the present case, the Federal Circuit's statement that Merck had not proved a greater than additive effect for sodium excretion was based on the district court's express finding that the combination of amiloride and hydrochlorothiazide produced a decrease in potassium excretion "without a reduction in the amount of sodium ions that are eliminated." (App. A at 9a.) That finding alone would have been sufficient to support the Federal Circuit's statement. However, the appellate court

The district court did find that the '813 patent did not teach "that amiloride and hydrochlorothiazide should be combined to produce the effects as set forth in the '430 patent." (App. B at 29a.) It made similar findings with respect to other prior art. (App. B at 32a.) That is very different from a finding that the patented composition actually achieved those results.

There is, of course, no dispute that the '430 patent *asserts* that the combination of amiloride and hydrochlorothiazide produces unexpected amounts of sodium excretion. However, *the overwhelming evidence established that the claimed combination did not in fact achieve these results* (App. E at 6a-14a, 16a-19a), and the district court so found (App. B at 18a). Consequently, a fair reading of the district court's opinion leads to but one possible conclusion: while that court found that the prior art does not suggest the results asserted in the '430 patent, it also found that the

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also referred to other findings made by the district court and to the lower court's refusal to adopt Merck's proposed finding. (*Id.*) Thus, in this case, unlike *Kelly*, the Federal Circuit's statement was fully supported by specific findings of the district court. That the position was also supported by the district court's refusal to adopt a proposed finding, does not support Merck's position.

Wholly aside from the foregoing, the statement was not even the basis for the Federal Circuit's decision. The statement appears in a portion of the opinion that recounts Merck's ever changing position. It notes that, at trial, Merck had contended that a greater than additive effect was obtained from the patented combination, but that Merck had abandoned that position on appeal. (App. at 9a.) Since Merck was not asserting on appeal that a greater than additive effect was obtained, the Federal Circuit's statement was pure dicta and had no bearing on its decision.

combination of 5 mg. of amiloride and 50 mg. of hydrochlorothiazide did not *in fact* produce unexpected results. The district court thus clearly rejected Merck's contention that the claimed combination actually achieved the unexpected increase in sodium excretion that is alleged in the '430 patent.[6]

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[6] Merck accuses the Federal Circuit of engaging in de novo fact finding when it allegedly stated that, given the teachings of the prior art, the co-administration of amiloride and hydrochlorothiazide was expected to "induce more sodium excretion then would either diuretic alone." (Petition at 17, 19.) Merck fails to advise this Court that the Federal Circuit's comment was made in response to Merck's argument that the evidence demonstrated that the claimed composition caused more sodium excretion than 50 mg. of hydrochlorothiazide alone and that this was an unexpected result. Significantly, as the Federal Circuit noted, this assertion was different than the one advanced by Merck below. (See App. A at 9a.) Thus, the statement in question is simply dicta which points out that, even if Merck's newly created position is correct, it would not impart patentability to the claimed invention.

Merck also characterizes as a de novo finding the Federal Circuit's statement that "the '813 patent instructs the artisan that any of the 1200 disclosed combinations will produce a diuretic formulation with desired sodium and potassium eliminating properties." (Petition at 16.) The assertion is utterly incredible since that fact was never disputed before the district court and that is precisely what the patent teaches when it states:

> It has also been found as another feature of this invention that when co-administered with other diuretic agents known to enhance the elimination of potassium ions along with sodium ions, the novel pyrazinoylguanidines of this invention will reduce the excretion of potassium ions and thus overcome this undesirable property of other diuretic agents. The compounds of this invention, therefore, are useful in

Merck urges two other alleged advantages of the amiloride-hydrochlorothiazide combination. First, it claims that the onsets and duration of action of the two compounds were well-matched, providing certain advantages. (Petition at 9.) Second, it asserts that one of the pyrazinoylguanidine compounds disclosed in the '813 patent (MK-685) was "totally inappropriate" for use in combination with hydrochlorothiazide (Petition at 9 n.3 and 16 n.9.)

There can be little doubt that these alleged "advantages" were induced by the present litigation. The '430 patent does not mention them. Although Merck had completed most of its clinical testing, including the testing of MK-685, the allegedly well-matched characteristics of amiloride and hydrochlorothiazide and the asserted incompatibility of MK-685 and hydrochlorothiazide were not mentioned while the applications that led to the '430 patent were before the PTO. To the contrary, MK-685 is one of the com-

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combination with other classes of diuretic agents to prevent the loss of potassium which the other diuretics would otherwise cause to be eliminated. [Column 3, lines 10-20.]

Moreover, Merck acknowledges that "[t]he '813 patent generally states that the pyrazinoylguanidines will reduce the excess potassium excretion caused by such other [potassium-losing] diuretics." (Petition at 9.) Finally, as noted *infra* at 21, Merck's expert deStevens has unequivocally asserted that the '813 patent suggests that the combination of amiloride and hydrochlorothiazide, the specific combination claimed in the '430 patent, would abate any excessive potassium loss that might otherwise result if hydrochlorothiazide were administered alone. Since hydrochlorothiazide was known to produce adequate sodium excretion, that is an admission that the combination would have desired sodium and potassium eliminating properties.

pounds which the '430 patent specifically states can be substituted for amiloride while still retaining the beneficial results of the patented invention. (Col. 2, ll. 46-55.)

Indeed, Merck did not introduce much evidence at trial concerning these alleged advantages until it became clear, following the testimony of its Medical Director in charge of the clinical studies with the amiloride-hydrochlorothiazide combination, that the alleged unexpected increase in sodium excretion was, in fact, nonexistent at the claimed dosage ranges. (App. E at 6a-14a.) Even then its position constantly shifted. In its first effort to prove that amiloride and hydrochlorothiazide were "well-matched," it urged that the two compounds had the same duration of action. After the evidence demonstrated that hydrochlorothiazide's duration of action was no more than half of amiloride's (App. E at 5a-6a), Merck changed its tune once again. It alleged, as it does now, that amiloride and hydrochlorothiazide were uniquely matched (App. E at 14a-15a).

These "advantages" are thus the type of litigation-induced pronouncements that this and other courts have consistently refused to accept as supporting unobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 25-26 (1966); *In re Vamco Mach. & Tool, Inc.*, 752 F.2d 1564, 1575 (Fed. Cir. 1985); *Schutt Mfg. Co. v. Riddell, Inc.*, 673 F.2d 202, 205 (7th Cir. 1982); *Carter-Wallace, Inc. v. Otte*, 474 F.2d 529, 540-43 (2d Cir. 1972), *cert. denied*, 412 U.S. 929 (1973); *Young Corp. v. Jenkins*, 396 F.2d 893, 895-96 (9th Cir. 1968).

C. The Federal Circuit Did Not Ignore The District Court's Finding Concerning Merck's Expert Witness

Merck correctly notes that the district court found that the testimony of its expert deStevens was "persuasive of the issue of obviousness as it related to the '813 patent." (Petition at 10.) But it wrongly asserts that the Federal Circuit did not accord proper deference to that testimony. (Petition at 19.) The only portion of the testimony that was relevant to the obviousness determination considered by the Federal Circuit supported the district court finding (adopted by the Federal Circuit) that the combination of amiloride and hydrochlorothiazide was one of 1,200 combinations described in the '813 patent. By way of example, in his expert report, deStevens stated:

> The '813 patent suggests that amiloride hydrochloride may be coadministered with hydrochlorothiazide to abate any excessive potassium loss that might otherwise result if hydrochlorothiazide were administered alone. [App. E at 21a.]

Moreover, while deStevens testified that the '430 *patent* taught that the amiloride-hydrochlorothiazide combination produced unexpected results, he never considered whether *the claimed composition* of 5 mg. of amiloride and 50 mg. of hydrochlorothiazide also produced unexpected results. He indicated that a sharp increase in sodium excretion over that which was achieved with hydrochlorothiazide alone would be an unexpected result. He was not prepared to state that only a slight increase in sodium excretion would be unexpected. (App. E at 1a-5a.)

Significantly, as demonstrated in the previous section, the district court rejected Merck's contention

that the claimed amiloride-hydrochlorothiazide combination produced an unexpected increase in sodium excretion. It instead found that the claimed combination "results in a reduction in the amount of potassium ions that are eliminated, without a reduction in the amount of sodium ions that are eliminated." (App. B at 18a.)

The testimony of Dr. deStevens thus *supported* the key findings of the district court which resulted in the Federal Court's reversal, that is that the '813 patent disclosed the amiloride-hydrochlorothiazide combination, albeit as one of 1,200 other possible combinations, and that the claimed composition did not produce an unexpected increase in sodium excretion.

D. The District Court Findings Regarding The Methodology Of Pharmaceutical Research And Lack Of Predictability Of Results In The Diuretic Field Are Also Irrelevant

Merck also alleges that the district court made explicit findings regarding how research was carried out in the pharmaceutical industry and the unpredictability of results in the diuretic field. (Petition at 13-14.) Those findings are, however, irrelevant because they are directed to prior art other than the '813 patent. There is no dispute that the '813 patent expressly teaches that any one of the disclosed pyrazinoylguanidines, one of which is amiloride, can be combined with any one of the disclosed potassium losing compounds, one of which is hydrochlorothiazide, to reduce potassium excretion caused by the potassium-losing compound. As noted in the previous section, Merck's expert deStevens specifically stated that the '813 patent "suggests" that the combination of amiloride and hydrochlorothiazide will "abate any

excessive potassium loss that might otherwise result if hydrochlorothiazide were administered alone." (App. E at 21a.) Indeed, before this Court, Merck acknowledges that the '813 patent generally states that the pyrazinoylguanidines [described in that patent] will reduce the excess potassium excretion caused by [potassium-losing] diuretics." It also concedes, as it must, that amiloride is one of the disclosed pyrazinoylguanidines and hydrochlorothiazide is one of the disclosed potassium losing diuretics. (Petition at 9.) The findings quoted by Merck are thus wholly irrelevant to the obviousness issue resolved by the Federal Circuit.

E. The Federal Circuit Did Not Ignore The District Court Finding That The Patented Product Was A Commercial Success

Merck urges that the district court made findings that the patented composition was a commercial success and notes that this evidence may support the validity of the patent. (Petition at 14.) The Federal Circuit, however, did not ignore that finding. In fact, it acknowledged the finding and noted that such evidence can be an indication of nonobviousness. It held however that, "in the circumstances of this case, where it is the only such indication, it is insufficient to render Merck's claimed invention nonobvious." (App. A at 11a n*.) That ruling is clearly consistent with the precedent of this court. *Sakraida*, 425 U.S. at 282 (the patented invention was obvious even though the invention was "doubtless a matter of great convenience, produced a desired result in a cheaper and faster way and *enjoyed commercial success. . .*" [emphasis added]).

V. THE FEDERAL CIRCUIT DECISION WILL NOT HAVE AN ADVERSE IMPACT ON PHARMACEUTICAL RESEARCH

Merck's allegation that the Federal Circuit decision in this case would somehow have an adverse impact on pharmaceutical research because of an alleged characterization of Merck's research effort as routine experimentation (Petition at 22-24) is plainly without foundation. In the first place, the Federal Circuit did not suggest that Merck's *entire* research effort was merely routine experimentation. As noted above, much of the research effort is wholly irrelevant to the obviousness analysis because it occurred long before the '813 patent disclosure became publicly available. The Federal Circuit's routine experimentation statement applied merely to the methodology used to determine that the commercial and patented composition would contain 5 mg. of amiloride and 50 mg. of hydrochlorothiazide.

In any event, the statement was not a finding of fact; it was merely a response to Merck's assertion that the specific amounts of each ingredient set out in the claims imparted patentability. In response to that argument, the Federal Circuit merely noted that the "evidence at trial showed that, though requiring time and care, the experimentation needed to arrive at the claimed dosages was nothing more than routine." (App. A at 10a.) The evidence to which the court referred was the testimony of Merck's own expert, deStevens. (App. A at 11a.) In its petition, Merck pointed to no evidence that the determination of the dosage ranges was anything but routine. Moreover, Merck fails to note that the tests, whether routine or otherwise, merely demonstrated that the claimed

composition achieves precisely the results that the prior art '813 patent teaches would be obtained. Discovering that the prior art teachings are correct is not an unobvious advance which warrants patent protection.

Finally, Merck's research efforts were more than adequately rewarded by the grant of the '813 patent. That patent gave it the right to be free from competition in the sale of an amiloride-hydrochlorothiazide product for seventeen years. The '430 patent extended that period of exclusivity an additional *six* years. Such an extension was clearly not justified by the minimal difference between the subject matter of the '813 and '430 patents.

Congress has decreed that an invention is entitled to only one patent for each patentable invention. 35 U.S.C. §§ 101-103. Research will not be impaired if, as in this case, that statutory decree is followed.

VI. CONCLUSION

For the foregoing reasons, Merck's petition should be denied.

Respectfully submitted,

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October 30, 1989

APPENDIX

[304] Goodfellow - direct

* * *

A. . . . Secondarily, the pharmacokinetics or the duration of action of both components was very nicely matched. So that the duration of hydrochlorothiazide was about 24 hours as was amiloride. There was a very nice fit. And a patient could take MODURETIC—virtually any patient could take MODURETIC once a day. And you can contrast that with dyazide where the duration of hydrochlorothiazide was longer than the duration of Dyrenium, their potassium spearer (sic), or ALDACTAZIDE where the duration of spironolactone to my recollection was much longer than hydrochlorothiazide.

So it didn't fit as well. We really had a true, once a day, antihypertensive product.

* * *

[437] de Stevens - cross

* * *

Q. Do you have the patent—the '430 patent in front of you, sir?

A. Yes. I believe you testified that the results reported in Tables 4 and 5 of the patent were unexpected?

A. Yes.

Q. They were unexpected because of the magnitude of the increase when the combination of amiloride and hydrochlorothiazide was administered on the sixth day of treatment; is that correct?

A. Under the conditions of this experiment.

Q. I'd like to ask you to make an assumption. What if the increase on the sixth day, when the hydrochlorothiazide plus amiloride were administered, was in your view min-

imal, the increase was minimal, would the result have been unexpected?

A. I can't answer the question.

Q. Why not, sir?

A. Because it is an assumption.

Q. You're an expert. I'd like you to make that assumption and answer the question based on the assumption?

A. Not consistent with the facts here. My testimony is based on these facts. My conclusions with regard to the unexpected effect is based on this.

Q. Doctor, I'd like you to assume, though, that the increase

[438] de Stevens - cross

that is obtained in sodium excretion when the combination of hydrochlorothiazide and amiloride are administered on the sixth day was minimal in your view. I'd like you to tell me, based on that assumption, whether you believe the results would have been unexpected?

A. That is a speculation. I don't know—under these same conditions, so on, I don't know what the point—in a speculative question of that type.

Q. I think it is important, sir. I'd like to have your opinion on that.

A. I wouldn't say it is unexpected or expected. I'd just look at it.

Q. You looked at the data in the patent and you said it was unexpected. Isn't that true?

A. Because of the nature of the experiment. We are starting with controls and we are carrying out this experiment over a five-day period giving a certain amount of hydrochlorothiazide per day.

We are—on the fourth and fifth day we are below control values. And then we give amiloride and we get a sharp increase in sodium excretion. That is unexpected.

Q. Well, sir, I'm asking you to assume all the facts you've just stated except one change. We don't have a sharp increase. Instead of the sharp increase we have an increase which is minimal. I would like to now know in your view, in your expert

[439] de Stevens - cross

opinion—you're an expert in this case, sir—whether that would be an unexpected result?

A. No, I don't think it would be unexpected or expected. I wouldn't know what to make of it.

BY THE COURT:

Q. Doctor, let's assume—take a look at Table No. 4, okay?

A. Yes.

Q. Let's assume under the sodium excretion?

A. Yes.

Q. You got it from 257 to 70 on the fifth day?

A. Yes.

Q. The next figure is 177.8. The next one after that is 160.2. Let's assume we get rid of the 100. If it was 77.8 and it was 60.2, would that be an unexpected result or an unexpected effect so far as you were concerned?

A. I would say that the amiloride was inactive.

Q. Would it be expected or unexpected?

A. I don't know until I carry out the experiment, sir. You see, I have to carry out the experiment. I get the result.

Q. This is the experiment. It is there?

A. Yes. I get 77—

Q. Instead of 177—you said it was unexpected that you got 177, correct?

A. Yes.

Q. Now I'm saying: Assuming it is 77, is that as equally

[440] de Stevens - cross

unexpected?

A. No.

Q. That would be expected?

A. No. It would show me that the compound may be inactive when mixed with hydrochlorothiazide.

THE COURT: Go ahead. Mr. Bajefsky.

(Pause.)

THE COURT: What if it went below 70 to 60?

THE WITNESS: I think I'd start to look at this very closely, this combination. Something is going wrong. In other words, it is totally inactive. It is doing nothing.

THE COURT: That would be unexpected?

THE WITNESS: I don't know until I carried out the experiment.

THE COURT: I'm saying: That is the experiment. You carried out the experiment. That is the length and breath of your experiment. Your experiment shows the figure to be 77 instead of 177.

You had no problem saying that when the number was 177 that was unexpected. Why was it unexpected?

THE WITNESS: Because what you had done over a period of five days was to give this dose of hydrochlorothiazide, 100 milligrams each day and you're depleting it

down below controls. And then when you give the amiloride you get a sharp increase.

[948] Mrozcek - direct

* * *

Q. Doctor, I'd like to return now to Exhibit 275. Again to the pages for MODURETIC. In particular, I would like you to read the two sentences beginning on the tenth line of the amiloride clinical pharmacology section.

A. We're on which page? 1322. 1322. Which line, sir?

Q. It's the tenth line of the amiloride clinical pharmacology section. It begins, "Amiloride"—

A. "Amiloride HCl usually begins to act within two hours after an oral dose. It's effect on electrolyte excretion reaches a peak between six and ten hours and lasts about 24 hours."

Q. I'd also like you to read the two sentences that begin on the seventh line of the hydrochlorothiazide clinical pharmacology section.

A. "The onset of diuretic action of hydrochlorothiazide occurs in two hours and a peak action in about four hours. Diuretic activity lasts about 6 to 12 hours. Hydrochlorothiazide is eliminated rapidly by the kidney."

Q. There has been testimony in this case that amiloride and

[949] Mrozcek - direct

hydrochlorothiazide have the same duration of action. Is that testimony correct?

A. Well, not according to the Physicians' Desk Reference information here.

Q. What does that tell you about the duration of action of these two drugs?

A. That hydrochlorothiazide lasts maximum 12 hours and the amiloride acts for 24 hours.

Q. Is there any advantage in amiloride having a duration of action from 12 to 18 hours longer than hydrochlorothiazide?

A. Not that I can imagine. The main use of amiloride should be to block the potassium excretion while the hydrochlorothiazide is working.

Q. Why is the main advantage of the amiloride while the hydrochlorothiazide is working?

A. Well, if one is looking to block potassium excretion, one wants to put potassium—the blockage of potassium excretion to occur while sodium is going through the tubule, as Dr. Preuss had pointed out. Actually, after the diuresis by the hydrochlorothiazide is over, there really isn't going to be any sodium in the distal tubule at the sodium-potassium exchange sites to be the amiloride or the potassium blocking agent to have any effect upon it.

[1018] Wilkinson - direct

* * *

Q. Now, isn't it further true that almost three years later than this document you concluded, you, yourself, concluded, not that the clinical studies established synergism, but that the studies demonstrated that the combination of amiloride and hydrochlorothiazide had the same overall pattern of safety and effectiveness as hydrochlorothiazide and that the only essential difference in action was on the serum potassium levels?

A. I have to see the context in which I made this conclusion.

Q. I'll show it to you. I'd like you to look at DTX-204.

A. Just a minute.

Q. Is this a document that you generated, Dr. Wilkinson?

A. It would appear to be so.

Q. And the date is July 29, 1969?

A. Yes.

Q. And it deals with the status of future studies for amiloride?

A. Yes.

Q. Okay. Now, I'm going to be reading something to you. I just want to know. CO-HydroDIURIL is the name that Merck had given at the time for amiloride in combination with hydrochlorothiazide?

A. Correct.

Q. And HydroDIURIL is hydrochlorothiazide alone. Correct?

A. Correct.

Q. Now, the last paragraph on the first page. I will read it. I'll read the first sentence of that paragraph.

It says, "In general, these studies demonstrate that CO-HydroDIURIL has the same overall pattern of safety and effectiveness as HydroDIURIL and that the only essential differences in action are upon serum potassium levels."

Did I read it correctly?

A. Correct.

* * *

[1020] Wilkinson - direct

* * *

Q. Is that a correct characterization of what you wrote at that time and what you believed at that time?

A. Apparently so.

Q. All right.

Now, when you are talking of these studies, am I further correct that the antecedent for that word are the studies earlier referred to in the first four paragraphs of that letter?

A. Yes.

Q. All right.

Q. So as of this date, what you were basically saying was, as I understand it, that the studies you had concluded demonstrated both from a safety and effectiveness standpoint that the only essential differences between the combination of amiloride and hydrochlorothiazide, as compared with hydrochlorothiazide alone,

[1021] Wilkinson - direct

was upon serum potassium levels; correct?

A. I have had a chance to read the memo.

Q. Please.

A. I think you have to put the last paragraph into, first, the context of—the purpose of its writing.

Q. Fine.

A. Dr. Robinson had assumed responsibility for the medical group, Dr. Lawrason having been given other responsibilities.

This page is attempting to encapsulate a tremendous amount of work that had already occurred. There were

two general phases of these studies. The earlier phases had been studies conducted by very well-known clinical investigators primarily using their own protocols and these studies tending to be in more seriously ill patients.

We had encountered a worrisome number of adverse findings. In particular, hyperkalemia would worry one with a drug of this nature. This could be a very dangerous adverse effect to a drug of this type.

Later studies, this second phase, which I referred to in the fourth paragraph down, the second generation of studies, we were purposely seeking less seriously ill patients in the so-called phase III type studies. And these were in—the results generally were comparable to the effects one might see with the thiazides. The adverse reaction frequency.

The doses that we had selected also were such that the

[1022] Wilkinson - direct

addition of these two drugs, the co-administration of these two drugs, gave effects both in terms of safety and efficacy that were not remarkably different from those that one would have seen with hydrochlorothiazide given alone.

Q. And that conclusion—correct me if I'm wrong—was reached on the basis of all of this data?

A. It was a summation by me for the man assuming responsibility for all the clinical studies of all the drugs and trying to get it down to one page.

Q. Isn't it true that this same characteristic in this last paragraph is applicable to the MODURETIC drug that is on the market today?

A. In general, I would believe it's very close to what we see with MODURETIC today. Yes.

* * *

[1027] Wilkinson - direct

* * *

Q. Fine. I would like you to look again at the exhibit we were talking about. I believe, at the end of the day, Defendant's Exhibit 204, which is in Volume 2. Do you have that exhibit?

A. Yes.

Q. We were looking at the last paragraph on the first page of that exhibit. Just so that we can get back to where we were, I will read again the first sentence of that paragraph. I will alert you to the fact that yesterday we read two sentences at the request of the Judge.

I want to ask you a question, one more question about the first sentence. I'll read it: "In general, these studies demonstrate that CO-HydroDIURIL has the same overall pattern of safety and effectiveness as HydroDIURIL and that the only essential differences in action are upon serum potassium levels."

Do you see that?

A. Yes.

Q. All I want to know now, to supplement what we covered yesterday in court, is that that includes—when you are talking about the same overall pattern of safety and effectiveness as HydroDIURIL, that includes sodium excretion, does it not?

A. It certainly is implicit in the statement.

Q. That is what you intended?

[1028] Wilkinson - direct

* * *

A. Yes.

* * *

[1036] Wilkinson - direct

* * *

Q. Now, on page 105689, which is the second page, paragraph 2—do you see that at the top of the page?

A. Yes.

Q. Now, just so the record will be clear. MK-870 is amiloride. Correct?

A. Correct.

Q. This paragraph, as I read it, says, "The diuretic effects of MK-870 are additive to those of hydrochlorothiazide and ethacrynic acid. And because of the antikaliuretic activity, this potentiation of diuresis can be accomplished without increased potassium secretion."

Did I read that correctly?

A. Yes.

Q. In fact, Dr. Wilkerson (sic), isn't it true that you ultimately concluded that your amiloride-hydrochlorothiazide combination was not effective even to provide significant additive natriuretic and diuretic results at practicably usable doses of amiloride?

* * *

[1037] Wilkinson - direct

* * *

A. Yes. But the doses that we utilized in the great bulk of studies were primarily to provide an additional information on the safe use of the drug.

I think we also knew—my recollection is that we always knew we could get significant enhancement of sodium excretion. But from a practical point of view, it would be at the expense of safety.

So that we kept the doses low, restricted. So the statement as it stands is I think an accurate one, that the drug behaved in terms of safety and effectiveness very similar to that of hydrochlorothiazide except that it did retain the potassium wastage that would have been associated with hydrochlorothiazide by itself.

So the answer is basically yes.

Q. Okay. Now, let me just refer you to DTX-191. That is in the first volume.

A. Right. I have it.

Q. Am I correct, Dr. Wilkerson (sic), that that is a document that you in the normal course of business would have generated on or about the date indicated?

A. I would assume so. Yes.

Q. And the date indicated, as I read it is, is July 19, 1968.

A. Correct?

Q. Now I'd like to read into the record the second paragraph of

[1038] Wilkinson - direct

that letter, but I would note if you feel you would like to read the entire letter, please feel free to so so. But the second paragraph reads as follows:

"Studies set up in 1965 and 1966 formed the basis for the New Drug Application with claims limited to three areas; hypertension, congestive heart failure, and cirrhosis with ascites," a-s-c-i-t-e-s. "Doses most commonly employed were 10 or 20 milligrams per day on a b.i.d. schedule. The objectives mandated by marketing requirements were effective antikaliuretic action when the drug was used with thiazides or more potent saluretic-diuretic agents and a sparing of dosage requirements of these agents. The first objective was achieved, but the second was not; hyper-

kalemia occurred at a prohibitively high rate at doses that were adequate to produce adequate additive and diuretic activity."

Did I read that correctly?

You're here talking about the combination of amiloride and other—and a thiazide?

A. And ethacrynic acid. Both combinations.

Q. That was actually hydrochlorothiazide, right?

A. Correct.

Q. Is this last sentence, here, this last statement.

"Hyperkalemia occurred at a prohibitively high rate at doses that were adequate to produce adequate additive, natriuretic and diuretic activity."

[1039] Wilkinson - direct

Was that statement the basis for your agreement with my question just a few minutes ago, that you finally concluded that your amiloride-hydrochlorothiazide combination was not effective even to provide significant additive natriuretic and diuretic results at practicably usable doses of amiloride?

A. Yes.

Q. And isn't it true that what would happen, if you used doses high enough to give you adequate additive natriuretic and diuretic activity, you would generate hyperkalemia in patients? Is that right?

A. You have to get back to the kind of patient you're talking about, too. It isn't a simple matter. But essentially you are correct.

Q. What would happen if they get hyperkalemia? They might die?

A. Yes.

Q. Therefore, it wasn't practicably usable at that rate?

A. The doses that are being discussed here are implicitly whether one would combine 5 or 10 milligrams of amiloride with 50 milligrams of hydrochlorothiazide. It's not stated, but as one sees, 10 or 20 on a twice daily schedule. 50 milligrams twice a day was the customary dose of hydrochlorothiazide.

So you're talking basically about a 5-50 or a 10-50 combination. And it was my strong feeling at the time that the 5-50 was a much more practical dose for wide use of the drug.

Q. Because while that wouldn't give you significantly additive

[1040] Wilkinson - direct

effects, it wouldn't create the hyperkalemia problem?

A. Correct.

* * *

[1335] Cragoe - direct

* * *

Q. Dr. Cragoe, would you turn to the next exhibit in your book, DTX-275?

A. Yes. I have.

Q. Dr. Cragoe, do you have Exhibit 275 before you?

A. Yes.

Q. In particular, would you look at page 1322? The page numbers are in the upper left-hand corner.

A. Yes. I have it.

Q. Can you tell me how soon after oral administration amiloride begins to work?

A. It says here amiloride-hydrochlorothiazide usually begins to act within two hours after an oral dose.

Q. When does amiloride reach its peak effect on electrolyte excretion?

A. The next sentence says: Its effect on electrolyte excretion reaches a peak between 6 and 10 hours.

Q. What is amiloride's duration of action?

A. The same sentence indicates it lasts about 24 hours.

Q. Now, Dr. Cragoe, when does hydrochlorothiazide begin to work following oral administration?

A. This indicates that the onset of diuretic action of

[1336] Cragoe - direct

hydrochlorothiazide occurs in two hours. And its peak action is in about four hours and that it lasts from 6 to 12 hours in its action.

Q. What do the onsets of activity times the peak action and durations of action of amiloride and hydrochlorothiazide mean as far as their suitability as diuretic drugs to be put together into a single composition?

* * *

A. Well, we felt this was virtually an ideal combination. The two drugs both begin their action at about the same time; that is, about two hours. They move along towards their peak at about the same rate. The action of amiloride continues a little after that after the hydrochlorothiazide is already over. Therefore, it is continually going to act against the potassium loss. And the entire effects are over within 24 hours permitting a one day—once a day use of the drugs.

DEFENDANT'S
EXHIBIT DTX-191

MEMO

TO	J.A. Page, M.D.	Location West Point
FROM	W.H. Wilkinson, M.D.	Location West Point
SUBJECT	Present Objective of MK-870 Clinical Studies	Date 7/19/68

You will recall that we recently briefly reviewed the present status of studies with Colectril and the two combinations presently under investigation. I felt that it might be useful for you to receive a distillation of our present plans for the clinical trial of this compound.

Studies set up in 1965 and 1966 formed the basis for the New Drug Application, with claims limited to three areas; hypertension, congestive heart failure, and cirrhosis with ascites. Doses most commonly employed were 10 or 20 mg./day, on a b.i.d. schedule. The objectives mandated by marketing requirements were effective antikaliuretic action when the drug was used with thiazides or more potent saluretic-diuretic agents and a sparing of dosage requirements of these agents. The first objective was achieved, but the second was not; hyperkalemia occurred at a prohibitively high rate at doses that were adequate to produce adequate additive natriuretic and diuretic activity.

* * *

M129335

DEFENDANT'S
EXHIBIT DTX-204

MEMO

TO:	Dr. H.J. Robinson	W 42-3
FROM:	Dr. W.H. Wilkinson	W 42-3
SUBJECT:	MK-870-Status of Future Studies	Date: 7/29/69

We are approaching completion of individual summaries of studies performed with Colectril® ,CO-HydroDIURIL® and CO-Edecrin® . Your remarks yesterday indicate that decisions as to the future of this family of drugs are to be considered by MSD in the immediate future.

* * *

In general, these studies demonstrate that CO-Hydro-DIURIL® has the same overall pattern of safety and effectiveness as HydroDIURIL® and that the only essential differences in action are upon serum potassium levels. At minimal added risk the potassium depletion that occurs with thiazide administration is averted.

M162548

DEFENDANT'S
EXHIBIT DTX-233

* * *

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-200
18-201

Jul 29 1981

Merck Sharp & Dohme Research Laboratories
Division of Merck & Co., Inc.
Attention: Charles P. Balant, Ph.D.
West Point, Pennsylvania 19486

Dear Dr. Balant:

Please refer to your new drug applications dated February 9, 1979 (18-200) and March 30, 1979 (18-201) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Midamor (amiloride hydrochloride, 5 mg) Tablets and Moduretic (amiloride hydrochloride, 5 mg and hydrochlorothiazide, 50 mg) Tablets.

* * *

M355207

* * *

Labeling should indicate clearly the risk of hyperkalemia and means of minimizing it, the limited dosage range that has been shown useful, the limited added diuretic or antihypertensive effect when amiloride is added to thiazides, and the limited basis for recommending prophylactic use of amiloride, and the lack of evidence that amiloride is a safe agent used alone, at least in most cases. We have attached labeling for amiloride revised to include this information, and also ask you to incorporate the following sections:

Indications

* * *

Amiloride has minimal diuretic or antihypertensive effects when added to a thiazide diuretic and is a weak diuretic/antihypertensive when used alone.

* * *

M355208

* * *

Sincerely yours,

/s/ M.J. Finkel

Marion J. Finkel, M.D.
Associate Director for
New Drug Evaluation
Bureau of Drugs

M355210

PLAINTIFF'S
EXHIBIT PTX-385

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

HON. DICKINSON R. DEBEVOISE

Civil Action No. 85-5585 (DRD)

MERCK & CO., INC.,

Plaintiff,

v.

BIOCRAFT LABORATORIES, INC.,

Defendant.

EXPERT REPORT
OF
GEORGE DESTEVENS

* * *

The '813 Patent

The '813 patent describes certain (3-amino-5,6-disubstituted-pyrazinoyl) guanidines as diuretic agents. Amiloride hydrochloride is specifically disclosed at Examples 89 (col. 31 and footnote, col. 38) and 207 (col. 49, 11. 25-40), and is the subject of claim 11 (col. 51, 1. 44). The specification states that the compounds of the invention when given alone "selectively enhance the excretion of sodium ions without causing an increase in excretion of potassium ions." (col. 2, 1. 65 to col. 3, 1. 2). It is further stated that "[i]t is also contemplated to combine compounds of this invention in unit dosage form with other known diuretic agents, such as, hydrochlorothiazide, ..." (col. 49,

11. 44-46). Example 208 (col. 49, 11. 52-67) describes the formulation of a capsule containing 50 mg of hydrochlorothiazide and 50 mg of (3-amino-5-isopropylamino-6-chloropyrazinoyl)-3,3-dimethylguanidine hydrochloride. The specification also teaches that, in combination with certain other classes of diuretic agents, the pyrazinoylguanidines will

- 16 -

reduce the loss of potassium ions caused by the other diuretics (col. 3, 11. 9-19).

This reference suggests that amiloride hydrochloride may be coadministered with hydrochlorothiazide to reduce the potassium loss that might otherwise be induced if hydrochlorothiazide were administered alone. The '813 patent does not, however, suggest that this combination would cause the unexpected results for sodium excretion and the ratio of sodium to potassium excretion that are achieved by the invention of the '430 patent. The results so described, therefore, would not have been obvious to one of ordinary skill in the art based on the teachings of the '813 patent.

* * *

- 17 -

* * *

August 14, 1987 /s/ George deStevens
Date George deStevens

- 30 -